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HISTORICAL MILESTONES

The Origin of Thrombolytic Therapy

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The origin of thrombolytic therapy is briefly reviewed. It began 40 years ago with the demonstration that the injection into patients of a partially purified activator of the native plasminogen-plasmin enzyme system was capable of dissolving clotted blood and fibrinous loculations in the chest. However, the application of this form of therapy for the dissolution of intravascular thrombi had to await a series of further developments, including extensive purification of the thrombolytic agents, evidence that plasminogen activators would be more appropriate than plasmin for thrombolysis and proof, first in animals and then in humans, that thrombi could be dissolved by the systemic administration of plasminogen activators.

The first study of thrombolytic therapy in acute myocardial infarction was reported in 1958. However, despite many studies conducted during the next 20 years, with encouraging reductions in mortality, thrombolytic therapy for acute myocardial infarction became established only when angiography provided visual evidence of the presence of a thrombus obstructing an infarct-related artery and of the achievement of prompt lysis with the administration of thrombolytic agents.

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Thrombolytic therapy began in 1946, when William S. Tillett and I began an investigation of the clinical potential of partially purified streptokinase preparations for dissolving clotted blood and fibrinous exudates in patients. We chose hemothorax and empyema cases to initiate our studies because serial radiographs would allow us to observe the effects and samples of fluid could be removed for analysis. In 1949, we published the first in vivo demonstration of the lysis of clotted human blood (1).

In Figure 1, the results, in early 1947, of the first therapeutic test of streptokinase in a patient are shown. The chest X-ray film is from a young man who had a loculated hemothorax after removal of the left lung and developed a high fever. We suspected an infection, but the small amounts of fluid that could be aspirated were sterile. By injecting 400,000 U of streptokinase into the chest, we attempted to determine whether it was possible to dissolve the hemothorax and expose the infection. The results were dramatic. Six hours after the injection, fluoroscopy revealed the breakdown of all the loculations and free mobility of the fluid in the chest. The chest X-ray film (Fig. 1) taken soon after the removal of 1,300 ml of lysed coagulum shows the pleural space drained of its previous contents. Fortunately, the fluid was sterile and the temperature spontaneously reverted to normal.

History of thrombolytic therapy. The history of thrombolytic therapy actually began in 1933 with the report by Tillett and Garner (2), which stated that Lancefield Group A beta-hemolytic streptococci isolated from patients produced a fibrinolytic substance. Tillett named this material streptococcal fibrinolysin. Although he envisioned that this substance ultimately could be used to dissolve fibrinous exudates, he did not have the training to attempt to isolate or purify this substance. His expertise was in bacteriology and infectious diseases. His laboratory, however, attracted good young investigators, and in 1941 Milstone (3) pointed out that a plasma factor, which he named "plasma lysing factor," was necessary for streptococcal-mediated fibrinolysis. In 1945, L. Royal Christensen (4), a microbiologist with good biochemical skills, worked out the mechanism of streptococcal fibrinolysis. He and MacLeod (5) pointed out that human plasma contained the precursor of an enzyme system, which he termed plasminogen, and that the streptococcal fibrinolysin, which he renamed streptokinase, was an activator or kinase that was capable of converting plasminogen to the proteolytic and fibrinolytic enzyme plasmin. They also pointed out that plasmin could digest fibrinogen as well

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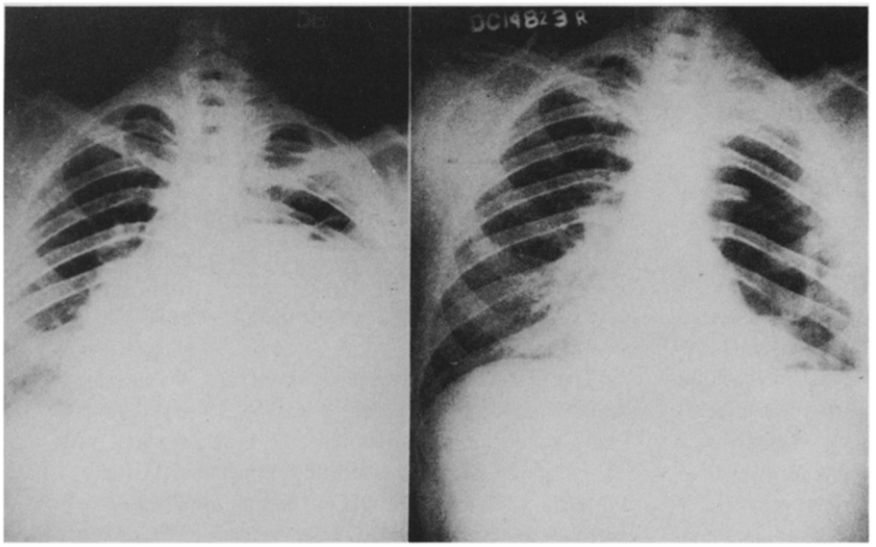

Figure 1. First demonstration in human patients of the efficacy of streptokinase in dissolving fibrin in loculated hemothorax for therapeutic purposes. See text for details. From Tillett and Sherry (1).

as fibrin, and that the action of plasmin was buffered by the presence of inhibitors in plasma.

In early 1947, Christensen (6) made available to Tillett partially purified preparations of streptokinase to be evaluated for their therapeutic potential in humans, and Tillett asked me to initiate the clinical investigation of this substance. Figure 2 is a photograph taken on a ward of New York City's Bellevue Hospital in 1949; Tillett, Christensen and I had been joined by Alan Johnson, a meticulous and dedicated investigator, and a research fellow, George Hazlehurst, who subsequently left us to enter private practice. Johnson was given the task of initiating studies on intravascular thrombolysis in experimental animals, while Hazlehurst worked with me on the clinical studies.

Studies on streptokinase. Initially, the streptokinase preparation, which was only 10% pure and contained a deoxyribonuclease, hyaluronidase and other streptococcal enzymes, was used to treat hemothorax (7), acute postpneumonic (8) and chronic empyemas (9) and to produce an enzymatic debridement of infected tissue spaces (10). Figure 3 is a photograph of a group of patients we treated successfully for a wide variety of conditions.

The major interest in the development of the clot-lysing ability of streptokinase, however, was based on its ultimate

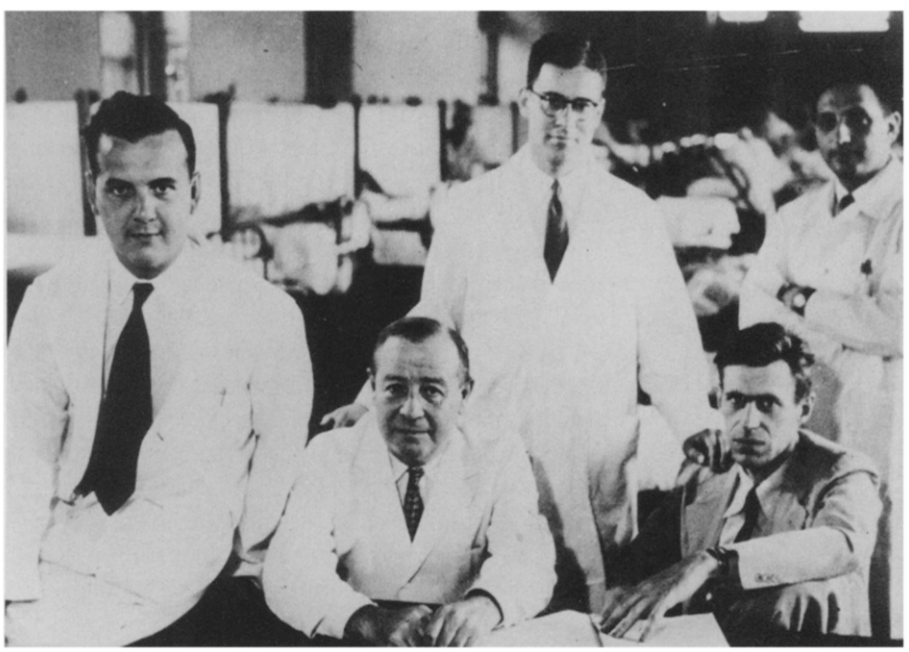

Figure 2. Team involved in the pioneering investigation of fibrinolytic therapy. Seated from left to right: George Hazlehurst, William S. Tillett and L. Royal Christensen. Standing from left to right: Alan Johnson and Sol Sherry.

Figure 3. Group of patients treated successfully for a wide variety of conditions with the enzyme preparation provided by Christensen. Hazlehurst (**left**) and Sherry (**right**) are shown examining the remnants of a chronic neck infection in one of the patients.

use in the treatment of acute coronary thrombosis. At the time, coronary thrombosis was a term used synonymously with acute myocardial infarction, a common medical problem with a ≥30% in-hospital mortality rate. The reason for this interest was that several well-known pathologists in the 1930s (11,12) and again in the 1960s and 1970s (13,14) had pointed out that the most common cause of a myocardial infarction was a thrombus superimposed on the cracked surface of an atheromatous plaque. However, our streptokinase preparations elicited severe febrile reactions when administered intravenously or injected into closed spaces. Though these preparations were not suitable for intravenous therapy, Lederle Laboratories initiated a program to develop preparations that would be acceptable for intravenous therapy, and in 1952, Johnson and Tillett (15) reported that experimental thrombi in rabbit ear veins could be lysed by the intravenous administration of streptokinase into a peripheral vessel.

Studies on plasminogen activator for thrombolysis. Shortly thereafter, Daniel Kline, then at Yale University, developed a technique that allowed for purification of human plasminogen (16). Because human plasmin could now be prepared in vitro by the addition of streptokinase, it was possible to consider human plasmin, rather than streptokinase, for thrombolysis. However, in vitro studies on clot lysis (17) indicated that the rate of fibrinolysis and its selectivity as a process were dependent on the presence of both a plasminogen activator and plasminogen, but not on plasmin alone.

The late 1950s proved to be a most productive period in the development of thrombolytic therapy. I was fortunate to be joined in St. Louis by two outstanding investigators, Tony Fletcher and Norma Alkjaersig, later to become Mrs. Fletcher (Fig. 4). First we attacked the problem of whether it would be best to use a plasminogen activator or the fibrinolytic enzyme plasmin. A variety of observations, both in vitro and in vivo (17–20), led us to conclude that plasminogen activators would be more successful as thrombolytic agents than would the proteolytic enzyme plasmin. This view was based mostly on the demonstration that the primary and most sensitive mechanism for thrombolysis was the penetration of an activator into a thrombus, with activation of the plasminogen that bound to fibrin during clotting (20). However, we knew that the intravenous infusion of a plasminogen activator like streptokinase would result in two different actions (Fig. 5). Diffusion of streptokinase into a thrombus would result in clot lysis, but the agent would also activate plasminogen in the systemic circulation, producing fibrinogenolysis and an impaired hemostatic mechanism.

Studies on streptokinase for thrombolysis. In the meantime, Lederle Laboratories had been successful in developing purified preparations of streptokinase that were well tolerated by patients and, in the absence of trauma or invasive procedures, with few bleeding complications. In 1957, we reported (21) on a rational approach to thrombolysis with streptokinase. It involved a loading dose and a sustaining infusion sufficient to increase the clot-dissolving activity of plasma several hundredfold and maintain a streptokinase concentration in plasma of about 10 μ/ml (Fig. 6, top panel). This resulted in a short-lived proteolytic state because, once the plasma plasminogen was exhausted, fibrinogen levels began to rise even though the streptokinase infusion was being maintained (Fig. 6, second panel). However, the clot-dissolving activity of the plasma was main-

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Figure 4. Team of investigators in St. Louis responsible for establishing the basis of plasminogen activators for thrombolytic therapy and for a variety of thromboembolic disorders including acute myocardial infarction. Shown from left to right are the late Anthony P. Fletcher, Norma Alkjaersig and Sol Sherry.

tained as long as streptokinase was being infused (Fig. 6, third panel). The therapy resulted in a prolongation of the prothrombin time (resulting from fibrinogenolysis) and the appearance of breakdown products (Fig. 6, bottom panel).

Johnson, who had remained in New York, demonstrated that a similar system was effective in dissolving experimental thrombi in human volunteers. An intravenous infusion into the opposite arm resulted, in most cases, in lysis of the clot and reestablishment of the patency of the vessel (Fig. 7).

First studies on acute myocardial infarction. The interest of our group, however, was to evaluate this regimen for clinical purposes, and in 1958, we reported (23) the first study of intravenously administered streptokinase in patients with acute myocardial infarction. The stated objective then, as now, was that "the rapid resolution of a coronary thrombus by enzymatic means could result in reduction of the final area of muscle infarction, reduction of the degree of electrical instability present during the early critical phase of infarction, and prevent the appearance of or lyse mural thrombi (23)." Ours was primarily a pilot study to determine how well the patient and the heart would tolerate a 30 h infusion of streptokinase.

Not only were we encouraged by the lack of complications we observed, but patients treated within the first 14 h after symptom onset had a very low in-hospital mortality

Figure 5. Dual effect of intravenously administered streptokinase. See text for details.

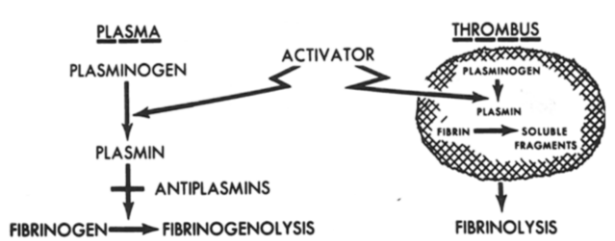
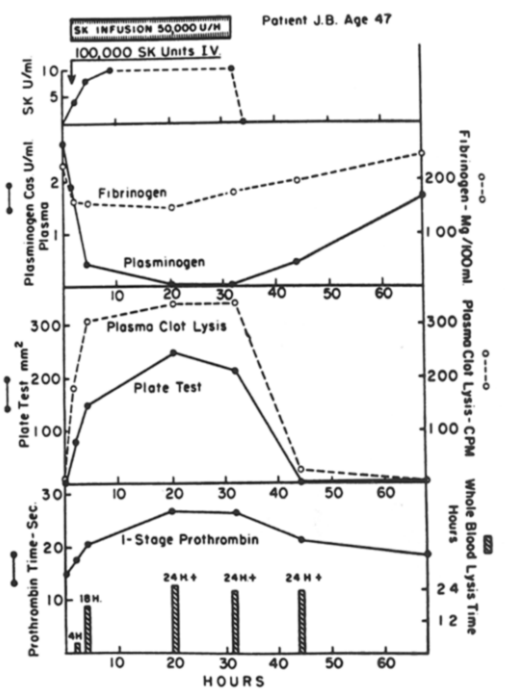


Figure 6. Serial biochemical determinations in a patient during a 30 h infusion of streptokinase (SK) administered intravenously. See text for details. From Fletcher et al. (24).



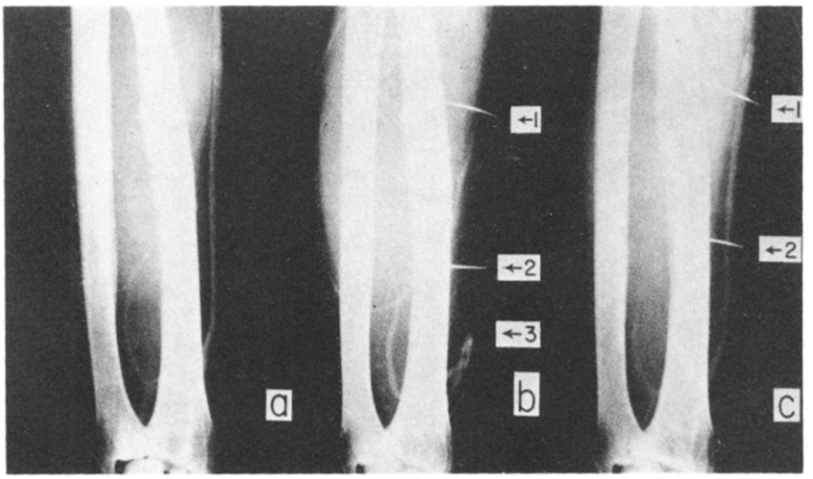


Figure 7. Radiographic demonstration of the lysis of an experimentally induced clot in a human volunteer. **Panel a**, control venogram before the induction of the clot showing a patent vessel. **Panel b**, venogram taken 24 h after the induction of a clot by traumatizing the intima of an antecubital vein by a dental burr inserted through a needle. The radioopaque lines at 1 and 2 were made by nichrome wires on the skin surface to define the extent of the clot; the **arrow** at 3 indicates the distal portion of the clot. **Panel c**, venogram 24 h after the streptokinase infusion, showing complete lysis of the clot without reformation. From Johnson and McCarty (22).

rate (Table 1), whereas patients treated anywhere from 20 to 72 h after symptom onset had a mortality rate similar to that of untreated patients. We also described (Fig. 8) the early peaking of serum transaminase in the streptokinase-treated patients (that is, at an average of 14 h rather than the 24 h as observed in untreated patients).

The details of these studies, which provided the basis for the use of plasminogen activators as thrombolytic agents as well as our pharmacologic and clinical observations on intravenous therapy with streptokinase, were published in 1959 (20, 24, 25) and attracted wide attention (26). As a result, a number of fellows who went on to become leaders in thrombosis research joined our research group. These included Nils Bang, Fedor Bachmann, who in 1964 while in our laboratory was responsible for the first major purification of a tissue plasminogen activator from pig heart (27), Robert Colman, Jack Hirsh, Heinz Joist, Zbigniew Latallo, George McNicol, Michael Mosesson, Josef Vermylen and Per Wallen. These fellows added much knowledge to the subject of fibrinolysis and helped in the clinical introduction of urokinase, a naturally occurring human activator whose preparation for clinical use was developed in conjunction with our group by Abbott Laboratories and Sterling-Winthrop (28).

Table 1. Mortality in Patients With Acute Myocardial Infarction Treated With Streptokinase

	No. Treated	No. Died
Early treatment (6 to 14 h)	15	1
Delayed treatment (20 to 72 h)	9	3

Results of a 30 h infusion of intravenously administered streptokinase when treatment was begun 6 to 14 h after the onset of symptoms of acute myocardial infarction or when therapy started 20 to 72 h later. From Fletcher et al. (23).

Lysis of pulmonary thrombi (urokinase and streptokinase). Pulmonary angiography was now an available technique, and this allowed for the demonstration of in vivo clot lysis of pulmonary emboli by urokinase and streptokinase as compared with heparin in National Institutes of Health-sponsored trials (29–31). Figure 9 shows the marked hypoperfusion on the right lung resulting from a large embolus in the right main pulmonary artery (left panel) and its disappearance within 24 h, with the restoration of lung perfusion after a course of thrombolytic therapy (right panel). These trials taught us that local factors were more important in determining the success of therapy than were measurable activities in the systemic circulation, and that bleeding complications were related to the lysis of hemostatic plugs at sites of vessel injury and were unrelated to the extent of the hemostatic defect induced in the patient.

Although a fixed dose regimen was introduced initially for urokinase, a great problem with the regimen we developed for streptokinase was that it required a considerable amount of laboratory control to determine the amount of the loading dose and then to adjust the sustaining infusion to maintain the desired level of activator activity in plasma. This problem was overcome by Verstraete et al. (32), who developed a standard dose therapy based on a loading dose that proved to be effective in overcoming the antistreptokinase resistance of ≥90% in treated patients, and a fixed maintenance dose that sustained a fairly intense clot-dissolving state.

When Lederle Laboratories ran into difficulties in quality control of streptokinase preparations, the 1960s and thereafter saw the production of streptokinase undertaken by Behringwerke in Germany and Kabi in Sweden. Table 2, which is based on a review by Yusuf et al. (33), lists 18 trials of streptokinase and 4 of urokinase administered intravenously for the treatment of acute myocardial infarction. These trials were conducted between 1963 to 1979, usually by a 24 h infusion and most often within 12 to 24 h after symptom onset. Though some of these trials were well

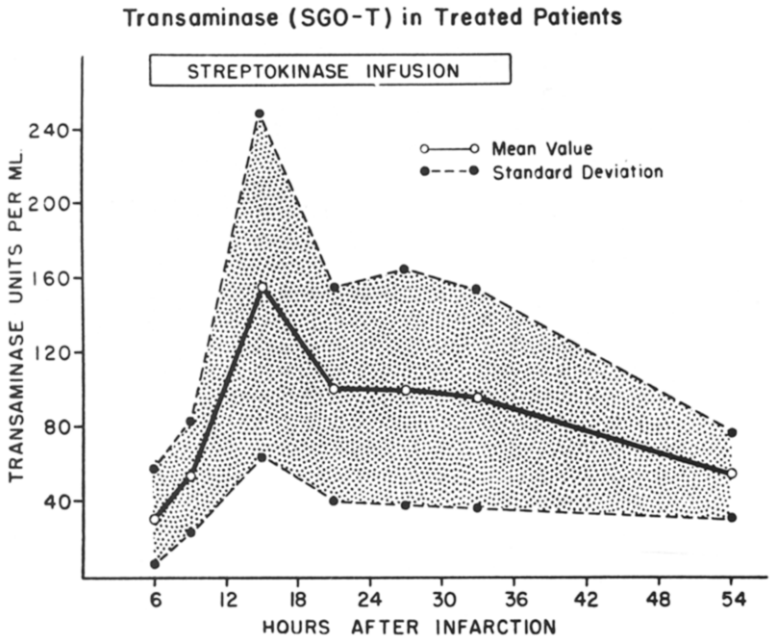


Figure 8. Serial serum glutamic oxaloacetic transaminase (SGOT) observations in patients after the onset of an acute myocardial infarction who were treated with a 30 h intravenous infusion of streptokinase. Note the early peaking of the serum transaminase at 14 h. From Fletcher et al. (23).

designed and conducted, for example, that of the European Cooperative Study Group (34,35), they were never taken seriously for the following reasons: 1) cardiologists no longer stressed coronary thrombosis as the cause of an acute infarct despite the view held by many leading pathologists on this subject during this period (36); 2) there were delays in admitting patients into trials because biometricians insisted that randomization be delayed until there were serial electrocardiographic changes and enzyme elevations; 3) coronary care units were coming into prominence, and most of the reported studies did not involve such units; 4) bleeding

Figure 9. Lysis of a large pulmonary embolus in the right main pulmonary artery by 12 h infusion of urokinase in the Urokinase-Pulmonary Embolism Trial (29–31). **Left panel**, pulmonary angiogram before treatment; **right panel**, pulmonary angiogram 24 h later (that is, after treatment). See text for details.

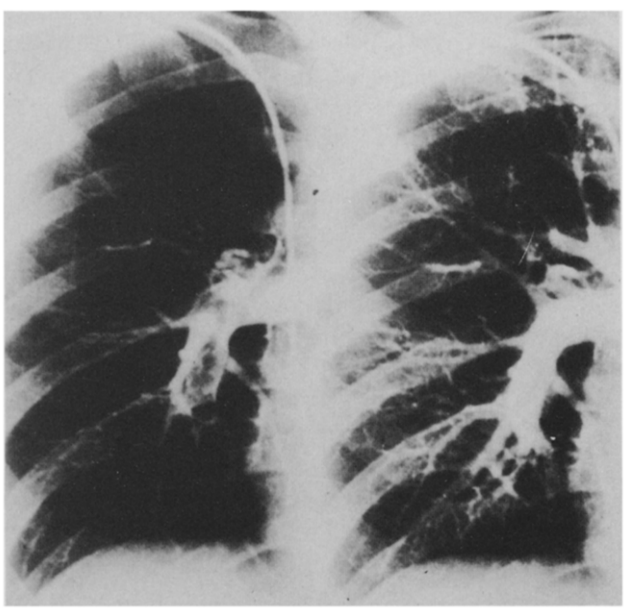


Table 2. Randomized Trials of Thrombolytic Therapy in Acute Myocardial Infarction Conducted Between 1959 and 1979 and Utilizing Sustained Intravenous Infusions of Streptokinase or Urokinase

Streptokinase	Urokinase
Fletcher et al. (1959)	Lippschutz et al. (1965)
Dewar et al. (1963)	Gormsen (1973)
Amery et al. (1967)	Brochier et al. (1975)
Heikenheimo et al. (1967)	European Collaborative Group (1975)
Dioguardi et al. (1971)	
European Working Party (1971)	
Bett et al. (1973)	
Breddin et al. (1973)	
Ness et al. (1974)	
Frank (1975)	
Valere et al. (1975)	
Klein et al. (1976)	
Aber et al. (1976)	
Australian (1977)	
Benda et al. (1977)	
Lasiera et al. (1977)	
Poliwoda et al. (1977)	
Wischitz et al. (1977)	
European Cooperative Study Group (1979)	

Adapted from review by Yusuf et al. (33), which also cites references. Year of the report is shown in parentheses.

complications became more frequent as the number of invasive procedures increased; and 5) there was no technique available for adequately measuring infarct size or ventricular function. Nevertheless, a retrospective meta analysis of these trials (33,37) indicated that overall there was a significant (approximately 20%) reduction in the mortality rate when the therapy, even though delayed, was carried out within the 1st day of infarction.

Besides these trials with intravenous therapy, efforts at directly infusing a fibrinolytic agent into the coronary arteries of patients suffering from an acute myocardial infarction began with the ingenious approach of Boucek and Murphy (38) in 1960. Subsequently, Chazov et al. (39) described its accomplishment by coronary catheterization in 1976.

Modern era thrombolytic therapy. This brings us to the modern era of thrombolytic therapy for acute myocardial infarction highlighted by: 1) its start by the demonstration by DeWood et al. (40) of a very high incidence of a total occlusion of the infarct-related artery when coronary angiograms were performed within the first 4 h after symptom onset, and the evidence that these occlusions were thrombotic; 2) the demonstration by Rentrop et al. (41) that local instillation of streptokinase into the thrombotically occluded vessel early after symptom onset brought about rapid recanalization in most cases; and 3) the subsequent introduction of a high dose, brief duration intravenous thrombolytic regimen by Schröder et al. (42) designed to accelerate the rate of thrombolysis and decrease the incidence of bleeding complications. In addition, there has been the development of a number of new plasminogen activators including prourokinase (43), recombinant tissue-type plasminogen activator (rt-PA) (44) and anisoylated plasminogen streptokinase activator complex (APSAC) (45).

Today, after a long developmental period, we are finally into the modern era of thrombolytic therapy for the initial treatment of an acute myocardial infarction. Ample evidence exists that the administration of a thrombolytic agent intravenously early after symptom onset will limit myocardial damage and reduce mortality.

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